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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/703,350	10/31/2000	Fuad Mehraban	10716-15 (CURA-90/P1891R1	3065

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EXAMINER	
YAO, LEI	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 10/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/703,350	MEHRABAN ET AL.	
	Examiner	Art Unit	
	Lei Yao, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *56 and 69-77* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *56 and 69-77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :3/23/01, 10/1/02, 9/2/04, 5/24/05, 2/1/06, 7/25/06 .

Response to Amendment

The Amendment filed on 7/25/06 in response to the previous Non-Final Office Action (4/25/06) is acknowledged and has been entered.

Claims 1-55 and 57-68 have been cancelled previously. Claim 56 has been amended. Claim 77 has been added. Claims 56 and 69-77 are pending and currently under consideration.

The text of those sections of Title 35, U.S.Code not included in this action can be found in the prior Office Action.

Information Disclosure Statement

The information disclosure statement (s) (IDS) submitted on 3/23/01, 10/1/02, 9/2/04, 5/24/05, 2/1/06, 7/25/06 are considered by the examiner and initialed copies/copy of the PTO-1449 are enclosed.

Objection/Rejections Withdrawn

1. The objection of specification because of containing an embedded hyperlink is withdrawn in view of the amendments to remove the hyperlink in the specification.

2. The rejection of claims 56 and 69-76 under 35 USC § 112 1st paragraph, as failing to comply with the written description requirement is withdrawn in view of the amendments to the claims, which no longer refers to an immunogenic fragment.

Rejection Maintained

Double patenting

Claims 56 and 69 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4, 9, and 10 of copending Application No. 10/824,075 for the reasons of record. Applicants request (page 5) that the Examiner hold this rejection in abeyance until notice of allowable subject matter (response filed 5/24/05). This request is noted, however, the rejection is maintained.

Under 35 USC § 112 1st paragraph—enablement

Claims 56 and 69-76 remain rejected and newly added claim 77 is also rejected under 35 U.S.C. 112 first paragraph, as failing to comply with the enablement requirement for the reasons of record in the prior Office Action dated 4/25/06 and state again as follows:

> Claims 56, and 69-76 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.
>
> Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:
>
> the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See also *Ex parte* Forman, 230 USPQ 546 (BPAI 1986).
>
> The claims are broadly drawn to a method of inhibiting angiogenesis in a mammal comprising administering to the mammal an effective amount of an antibody or antigen binding fragment thereof that specifically binds and neutralizes a polypeptide comprising SEQ ID NO:76 or binds to an immunogenic fragment of SEQ ID NO:76.
>
> The specification teaches that SEQ ID NO:76 is a secreted glycoprotein referred to as a stanniocalcin precursor (page 25). The specification proposes that "neutralizing antibodies to stanniocalcin may be useful as therapeutic molecules because they bind to stanniocalcin and thereby remove it from the immediate cellular environment". Thus, the specification appears to broadly claim that the claimed antibodies would predictably provide a therapeutic benefit to humans in need of reducing angiogenesis. For example, the specification teaches that angiogenesis is an important component of a variety of diseases and disorders including tumor growth and metastasis, rheumatoid arthritis, psoriasis, diabetic retinopathy, neovascular glaucoma, etc. (page 12). Thus, the claims broadly encompass methods of treating cancer by administering an antibody that binds to SEQ ID NO:76. However, the specification lacks critical guidance and objective evidence to predictably enable those of skill in the art to practice the invention with success. For example, there is no evidence that inhibition of stanniocalcin activity or removal of the secreted glycoprotein of SEQ ID NO:76 results in the inhibition of angiogenesis with concomitant reduction of tumor cell growth in a mammalian subject. There is no guidance that selective binding of SEQ ID NO:76 with an antibody would predictably reduce tumor cell growth or metastasis in a mammalian subject. The state of the art of reducing tumor cell growth and inhibiting other disorders associated with angiogenesis is highly unpredictable.
>
> For example, it was recently revealed that the drug Endostatin is unlikely to be the kind of across-the-board cancer cure that many had hoped for. Out of the 61 terminally ill patients tested, not one recovery had been seen (MSNBC News Services, "Mixed results on new cancer drug", November 9, 2000). Thus, just with regards to inhibiting angiogenesis in general, there is a high standard of accountability recognized by those in this particular area. Based on the very little guidance in the specification, one of skill in the art would not immediately presume that the antibodies would successfully reduce angiogenesis.
>
> Moreover, the pharmaceutical administration of antibodies for the treatment of tumors requires a high degree of guidance as those of skill in the art recognize the unpredictability of treating mammals (including mammals with tumors) via the administration of antibodies. Jain (Scientific American July 1994), discloses several barriers to the delivery of drugs into solid tumors including large molecular weight drugs such as antibodies. The impediments include (1) Non-uniform blood delivery to all areas of the tumor in which some areas of the tumor receive therapeutic agents and other areas of the tumor receive no therapeutic agent at all. (Page 60 col. 3); (2) Increased viscosity of blood in the tumor itself which also hinders drug delivery to the tumor (see paragraph bridging pages 60 and 61); (3) High liquid pressures in the interstitial matrix can retard the delivery of large therapeutic agents, **such as antibodies**, into tumors (page 61, Col. 1 paragraph 1); (4) Convection is a necessary mechanism by which larger therapeutics molecules such as antibodies, reach target cells which are not directly fed by the vasculature. Convection is not observed in large tumors (defined as more than ½ centimeter in diameter, page 62 col. 1) and convection is necessary for adequate drug delivery of molecules having a molecular weight of more than 5000 (page 61, col. 1 through page 63, col. 3) and (4) Molecules as large as antibodies (i.e., MW=150,000) would require

several months to reach a uniform concentration in a tumor that measures 1 centimeter in radius (page 63, col. 2). Further, treatment of cancer in general is at most unpredictable, as underscored by Gura (Science, v278, 1997, pp.1041-1042) who discusses the potential shortcomings of potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with clonogenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, 1st column) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive. All of this underscores the criticality of providing workable examples which is not disclosed in the specification, particularly in an unpredictable art, such as cancer therapy. Thus, despite evidence that expression of the stanniocalcin gene is upregulated under endothelial tube-forming conditions, the specification offers no guidance and or objective evidence that "inhibiting" or neutralizing this activity in a mammal would effectively inhibit angiogenesis.

In view of the teachings above, and the lack of guidance and or exemplification in the specification, it would not be predictable that the method would function as contemplated. Thus, it would require undue experimentation by one of skill in the art to practice the invention as claimed.

The response filed 7/25/06 has been carefully considered but is deemed not to be persuasive. The response states that applicants have provided a working example showing upregulation of stanniocalcin precursor in endothelial cell undergoing tube formation and provided references showing that endothelia cell model of tube formation is an art recognized mode for angiogenesis. Applicants further argue that the Office failed to provide any evidence that the endothelial model for tube formation does not correlate to angiogenesis. In response to the arguments, the Office agree that in vitro endothelial model of tube formation is provided in the specification (page 133) and correlation of the angiogenesis with increased expression of stanniocalcin have been recognized by one skilled in the art. However, in this application, Applicants claim a method for inhibiting angiogenesis in a mammal by administering an effective amount of an antibody or antigen binding fragment thereof to neutralize stanniocalcin precursor protein. Although, the specification teaches a working example showing upregulation of a stanniocalcin precursor in endothelial cells (example 19), there is no objective evidence provided by the instant application indicting that inhibition of stanniocalcin activity or removal of the protein by administering an antibody or antigen binding fragments in a mammal results in the inhibition of angiogenesis or reduction to tumor growth associated with angiogenesis. Because of unpredictability of treating angiogenesis associated tumor and cancer therapy with antibody to specific antigen, providing objective evidence, such as working examples, to support claimed invention in the disclosure are critical and necessary for enabling one skilled in the art to make and/or use the invention. Since applicants have not provide such exemplification in the specification, since the disclosure lacks guidance, and since the

claimed method is not predictable, one skilled in the art would be forced into undue experimentation to practice the claimed invention. Thus, Applicant's argument has not been found persuasive, and the rejection is maintained.

Conclusion

NO claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Olsen et al., (US Patent Appl, pub, US2002004237A1, 10/27/999) teach a method treatment of diseases or disorders associated with neovascularization by administration of the stanniocalcin polynucleotides and/or polypeptides of the invention, as well as agonists or antagonists of stanniocalcin (para 422). Olsen et al., do not specifically teach or suggest that upregulation of stanniocalcin is associated with angiogenesis or angiogenetic tumor. Olsen et al., do not teach or suggest a method of inhibiting angiogenesis by administering an antibody to stanniocalcin.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lei Yao, Ph.D. whose telephone number is 571-272-3112. The examiner can normally be reached on 8am-6.00pm Monday-Thursday.

Any inquiry of a general nature, matching or file papers or relating to the status of this application or proceeding should be directed to Kim Downing for Art Unit 1642 whose telephone number is 571-272-0521

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lei Yao, Ph.D.
Examiner
Art Unit 1642

LY

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER